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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,422	03/27/2006	Birke Bartosch	P08575US00/BAS	4780

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
02/04/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,422	BARTOSCH ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-91* is/are pending in the application.

4a) Of the above claim(s) *57,67,71-81 and 88-90* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-56, 58-66, 68-70, 82-87 and 91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/11/2009 has been entered.

Claims 1-45 have been cancelled. Claims 57, 67, 71-81 and 88-90 have been withdrawn. Claims 46, 59, 70, and 84 have been amended.

Claims 46-56, 58-66, 68-70, 82-87 and 91 are under examination.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 46-56, 58-66, 68-70, 82-87 and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marasco et al. (WO 00/55335, of record), in view of both Lechmann et al. (Hepatology, 2001, 34: 4117-423, of record) and Ray et al. (FEMS Microbiology Letters, 2001, 202: 149-156, of record).

Marasco et al. teach an *ex vivo* method of producing infectious virus-like particles such as a flavivirus-like particle by **(i)** providing a packaging retroviral vector comprising a transgene and the cis-acting elements necessary for encapsidation, reverse transcription, and integration (i.e., a first nucleic acid sequence comprising a packaging competent retroviral genome), a vector encoding the retroviral gag-pol (i.e., a second vector comprising a cDNA encoding retroviral core proteins), and a vector encoding the flavivirus envelope proteins (i.e., a third nucleic acid sequence comprising a cDNA encoding the envelope proteins), and **(ii)** transfecting host cells with the vectors above, culturing the transfected host cells to express the viral proteins and form the viral particles (claims 46, 48, 58, 70, and 84) (p. 4, third full paragraph, p. 6, first and second full paragraphs, p. 7, first paragraph, p. 16, p. 12, first and third paragraphs, p. 34, last paragraph, p. 41, third and fourth full paragraphs, claims 1-3 and 6-12). Marasco et al. also teach purifying their viral particles and using them to induce immune responses or to deliver transgenes to cells (claims 59, 82, and 83) (p. 34, last paragraph, p. 35). Although Marasco et al. teach their method as suitable to make infectious flavivirus-like particles, they do not specifically teach HCV, nor do they teach a HCV polyprotein comprising in order the core protein, the native E1 and E2 proteins, and the native p7 protein (claims 46-56, 58-66, 68-70, 82-87, and 91). Lechmann et al. teach obtaining infectious HCV-like particles wherein the HCV-like particles are made by using a vector encoding a polyprotein comprising successively the HCV core, E1, E2 and p7 proteins (Abstract, p. 417, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Marasco et al. by using the

polyprotein of Lechmann et al. to achieve the predictable result of obtaining infectious HCV-like particles. By including HCV core protein, one of skill in the art would have necessarily included a signal sequence because the HCV core protein comprises a signal sequence, wherein the signal sequence is required for the proper polyprotein targeting to the host cell endoplasmic reticulum (see Ray et al., p. 150, column 1 and Fig. 1). With respect to the limitation of a signal peptide derived from a type I membrane protein (claims 46 and 70), it is noted that the instant claim 70 defines that the signal sequence from a type I membrane protein could be the signal sequence from the core protein. Therefore, the combined teachings of Marasco et al. and Lechmann et al. disclose an infectious HCV-like particle obtained by using a nucleic acid sequence comprising a cDNA encoding a polyprotein containing successively a signal peptide from a type I protein, and the HCV E1, E2, and p7 proteins. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicants argue that, as indicated in the instant specification, viral particles of the prior art were obtained with chimeric E 1 and E2 glycoproteins having transmembrane domains that were modified to allow them to be trafficked to the cell surface. See page 2, lines 8-11 of the application-as-filed. In this regard, Applicants submit further evidence that one of ordinary skill in the art would have understood that pseudotyping was only possible with modified E 1 and E2, including the following references submitted herewith: Matsuura et al. (2001) Virology 286:263-75 ('°Matsuura"), and Buonocore et al. (2002) J. Virology 76, 14:6865-72 ("Buonocore").

As shown in these references, one of ordinary skill in the art at the time of the invention would have understood that HCV E 1 and E2 proteins include retention signals in their C-terminal transmembrane domain, which would prevent their expression at the cell surface. See Matsuura, page 264, 1st column, 2nd paragraph; see also Buonocore (describing modification of HCV E1 and E2 proteins to enable the expression of E1 and E2 proteins at the cell surface). Accordingly, one of ordinary skill in the art would not have had a reason to combine Marasco, Lechman, and Ray with any reasonable expectation of success in producing HCV-like particles in accordance with the present invention. Indeed, it would have been understood that such pseudotyping was only possible with modified E 1 and E2 devoid of retention signals, which would have taught away from the present invention. Applicants thus submit that the present invention is not rendered obvious by the Marasco, Lechmann, or Ray references, either singly or in combination, and that the claims of the present application relating to a method for producing infectious hepacivirus-like particles are clearly patentable over those references. Applicants thus submit that the Examiner's rejection on the basis of those references should be withdrawn.

Applicant's arguments are acknowledged; however, they are not found persuasive for the following reasons:

Applicant's arguments and cited references all pertain to pseudotyped VSV particles. Such arguments and evidence are not material to the instant rejection because the instant rejection is related to obtaining flavivirus particles (HCV is a

flavivirus) and not to obtaining pseudotyped VSV particles. As opposed to producing pseudotyped VSV particles, which requires expressing E1 and E2 on the cell surface, producing HCV-like particles requires the retention of E1 and E2 in ER; E1 and E2 do not need to be expressed on the cell surface to be incorporated into HCV-like particles (Ezelle et al., J. Virol. 2002, 76: 12325-12334, of record; see p. 12327, column 2; Dubuisson et al., J. Virol., 1996, 70: 778-786, p. 784, column 2). The prior art teaches that using a nucleic acid encoding a polyprotein comprising the core, E1 and E2 proteins results in properly processed E1 and E2 followed by their successfully incorporation on the surface of HCV-like particles (see Lechman above; Ezelle et al., J. Virol., 2000, 76: 12325-12334, of record, see Abstract, p. 12326, Fig. 1, p. 12327, column 1). One of skill in the art would have expected to be reasonably successful in producing HCV-like particles by combining the teachings of Marasco, Lechman, and Ray. For these reasons, Applicant's arguments are not found persuasive and the rejection is maintained.

Conclusion

4. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Dubuisson et al. (J. Virol., 1996, 70: 778-786) was cited in response to Applicant's argument that one of skill in the art would not have had a reason to combine Marasco, Lechman, and Ray. Specifically, the reference provides evidence that one of skill in the art would have known that combining Marasco, Lechman, and Ray would result in the successful production of HCV-like particles.

5. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633